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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LAM, ANN Y	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 12/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/985,873	BURANDA ET AL.	
	Examiner	Art Unit	
	Ann Y. Lam	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-73* is/are pending in the application.

4a) Of the above claim(s) *69-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 12, 2006 has been entered.

Election/Restrictions

Newly submitted claims 69-73 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Newly submitted claims 69-73 (Invention I) are directed to a method, classified in class 435, subclass 4, whereas claims 54-72 (Invention II) are directed to a device, classified in class 436, subclass 518.

Inventions I and II are related as process and apparatus for its practice. The inventions are distinct if it can be shown that either: (1) the process as claimed can be practiced by another and materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. (MPEP § 806.05(e)). In this case, the apparatus can be used to practice another and materially different process such as purification for subsequent use. That is, the apparatus can be

used without detecting a pre-complexing fluorescent signature and a post-complexing fluorescent signature.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art in view of their different classification, restriction for examination purposes as indicated is proper.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 69-73 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 54-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 54, line 5, and claim 63, line 4, recite "a first biomolecule bound to each bead in the first population". One interpretation is that a first *type* of biomolecule is bound to each bead in the first population. Another interpretation however is that one biomolecule is bound to each of the beads in the first population. Thus, it is unclear as to which interpretation Applicants intended. For examination purposes, the claim is interpreted according to the first interpretation.

The same ambiguity occurs in line 9 of claim 54, and in line 10 of claim 63, regarding the second biomolecule in the second population, which will be interpreted similar to the interpretation regarding the first biomolecule as stated above.

Similarly, claim 54, line 6, and claim 63, line 4, recite "a first fluorescent tag bound to each biomolecule". One interpretation is that a first type of fluorescent tag is bound to each biomolecule in the first population. Another interpretation however is that one fluorescent tag is bound to each biomolecule in the first population. Thus, it is unclear as to which interpretation Applicants intended. For examination purposes, the claim is interpreted according to the first interpretation.

The same ambiguity occurs in line 10, of claim 54, and line 11 of claim 63, regarding the second fluorescent tag in the second population, which will be interpreted similar to the interpretation regarding the first fluorescent tag in the first population.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 54-57 and 62-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Myers, 6,267,884, in view of Efimov et al., 7,115,738, and further in view of Chandler et al., 6,268,222.

Myers teaches the invention substantially as claimed. More specifically, as to claim 54, Myers teaches a chromatography column (46) with beads of different surface chemistries (48, 50), with one type of chemistry disposed within one region of the column and another type of chemistry within an adjacent region of the column in order to separate analytes (col. 4, lines 45-60, and see figure 4). Thus, Myers teaches a first and second population of beads with different biomolecules attached and with the population of beads being in regions distinct from each other, as claimed by Applicant.

However, Myers does not teach use of different tags on the different biomolecules. Efimov et al. in view of Chandler et al. however teach these limitations.

Efimov et al. teach use of capture probes on beads for separation (col. 51, lines 12-16 and line 66 – col. 52, line 2). Efimov et al. also teach that after separation, the separated molecules can be detected or analyzed (col. 50, lines 55-56). Moreover, it is

taught by Efimov et al. that the capture probes can optionally include a detectable label, such as a reporter group (col. 52, lines 5-6). Detectable label or reporter groups as used by Efimov et al. include fluorescent labels (col. 6, lines 3-5, and col. 10, lines 56-58). It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide a label, such as a fluorescent label, on the capture probe in the Myers invention, as taught by Efimov et al., because Efimov et al. teach that such labels provide the benefit of detecting or analyzing the molecules after separation. However, Efimov et al. do not teach use of different labels on different beads.

Chandler et al. however teach use of different fluorescent dyes on different particles such that each particle has a unique emission spectra and thus subpopulations of analytes of interest can be detected by various means (see col. 3, lines 4-9, and col. 4, lines 51-67, and col. 9, lines 41-50). Chandler et al. teach that the fluorescent article of the invention can be used for coupling of biological material for assays and affinity purification and separation (col. 12, lines 58-64). It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide different fluorescent dyes on the different beads in the Myers' invention, as taught by Chandler et al., because Chandler et al. teach that use of different fluorescent dyes on different beads functionalized with different biological material provide the benefit of detecting different materials, in addition to separating the materials. It is noted that while Chandler et al. utilizes a different means, nanospheres, to attach the dye to the bead, and do not teach the dye is coupled *to the biomolecule,* this limitation is taught by Efimov et al. as

discussed above, and Chandler et al. is relied upon for the teaching of using different dyes for detection of subpopulations of analytes.

As to claims 55 and 56, Myers discloses that the beads with different surface chemistries (48, 50) are in regions one on top of the other in the column (see col. 4, lines 45-60, and figure 4), and thus the analyte is initially exposed to only the first population of beads and subsequently to only the second population of beads

As to claim 62, Myers does not teach that the first biomolecule is any particular type of molecule, such as an antibody, protein or DNA sequence, but rather teaches beads with surface chemistries in general (col. 2, lines 42). However, Efimov et al. teach DNA probes on beads for hybridization and separation of DNA (from a sample), (col. 51, lines 12-16). It would have been obvious to one of ordinary skill in the art to provide DNA probes as the surface chemistries on the Myers beads, as taught by Efimov et al., because Efimov et al. teach that the DNA probes provide the benefit of hybridizing to and separating DNA from a sample.

As to claim 63, Applicants further claim that the device is a microfluidic device having a plurality of microfludic channels wherein at least one of the channels comprises the different populations of beads. Myers discloses that the device is a capillary liquid chromatography column (col. 2, lines 10-11) and that capillary liquid chromatography columns are a micro-version of the traditional liquid chromatography, and typically include a micro-pumping unit and a detector, and the diameter of the capillary column is typically in the micrometer range (col. 1, lines 51-52 and lines 57-60 and line 65-67). Myers discloses that the capillary column of the disclosed invention is in

the micrometer range (col. 3, line 65 – col. 4, line 2). Thus the capillary column disclosed by Myers is considered to be a microfluidic channel because it is small, in the micrometer range, and it is used for fluid flow. Moreover, different portions of the capillary column is considered to be different channels and thus the Myers device is considered to be comprised of a plurality of microfluidic channels. It is noted that "channels" according to Applicants' claims can be contiguous.

As to claim 64, one channel comprises at least one biomolecule that is different from the biomolecule in the first channel (see Myers, col. 4, lines 45-60, and see figure 4).

As to claim 65, one population of beads is considered to be layered over the second population of beads (see Myers, col. 4, lines 45-60, and see figure 4). It is noted that Applicants' specification does not require a particular orientation of the population of beads other than that they are adjacent to each other, and thus "layered over" is considered to mean adjacent.

Claims 57 and 66, Myers discloses indentations positioned along the interior of the column's channel at intervals corresponding to approximately half the diameter of the particle bead used to pack the column in order to stabilize the positioning of the particle bead once disposed within the channel (col. 2, lines 26-32). The particles are also monodispersed (see col. 2, line 11). Myers discloses that at least one particle bead is positioned between a set of indentations (col. 2, lines 31-32). Thus with the modification of the Myers' invention in view of Efimov et al. and Chandler et al., the

different populations are going to be separated by an obstructive feature, i.e., the last obstructive feature of the last bead of one of the populations.

As to claim 67, Myers disclose an inlet (col. 4, line 30).

2. Claim 61 is rejected under 35 U.S.C. 103(a) as being unpatentable over Myers, 6,267,884, and Efimov et al., 7,115,738, and Chandler et al., 6,268,222, as applied to claim 54 above, in light of Hopp et al., 4,851,341.

Myers in view of Efimov et al. and Chandler et al. teach the invention substantially as claimed (see above regarding claim 54).

As to claim 61, Applicants further claim that the first biomolecule comprises the amino acid sequence DYKDDDDK. Myers does not teach use of this amino acid sequence.

It is noted that this amino acid sequence is the same as the term "flag" as used in the art, see Hopp et al. (col. 2, line 40). Also, the use of this amino acid sequence, or flag, is taught by Efimov et al. (col. 51, line 64). More specifically, Efimov et al. teach use of flag tag sequence on a capture probe to bind to a solid support such as a bead (col. 51, line 58 - col. 52, line 2). It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the flag sequence as taught by Efimov et al. in the capture probe in the Myers invention because Efimov et al. teach that the flag sequence is useful for binding a capture probe to a solid support bead

(such as the bead in the Myers invention). It is noted that use of the flag sequence for binding a capture probe is also disclosed by one of Applicants' embodiment.

3. Claims 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Myers, 6,267,884, in view of Efimov et al., 7,115,738, and further in view of Chandler et al., 6,268,222, as applied to claim 54 above, and further in view of Craig et al., 6,972,198.

Myers in view of Efimov et al. and Chandler et al. teach the invention substantially as claimed (see above), except for the first and second fluorescent tags initially having a pre-complexing fluorescent signature and upon binding between the first or second biomolecule and an analyte, the first or second fluorescent tag associated with the analyte-bound biomolecule has a detectable post-complexing fluorescent signature. However, fluorescent tags having a pre-complexing fluorescence and a post-ccomplexing fluorescence is taught by Craig et al. as further explained below.

Craig et al. teach a modified, or alternatively an unmodified, protein, for example, a phosphorylated protein or unphosphorylated protein (col. 16, lines 12-41). Craig et al. teach constructing a peptide partner that will bind the protein whether it is modified or unmodified (i.e., in both conformation states), and a second peptide partner which can bind to the substrate only if it is modified by binding to a newly exposed surface on the modified protein based on specific sequence recognition. Craig et al. teach that these

two peptides can be labelled with appropriate fluorophores (e.g., fluoroscein and rhodamine) which will exhibit Fluorescence Resonance Energy Transfer (FRET) when they are in close proximity. Craig et al. teach that when the substrate is unmodified, only the first peptide will bind. If the protein however is modified, such as by a kinase or a phosphatase, the second peptide will bind to a binding motif that was unmasked by the modification or conformation change, and thus the assay can distinguish between the unmodified and modified states of the protein (col. 16, lines 12-16). Craig et al. teach that in a FRET assay of the invention, fluoresecent labels are chosen such that the excitation labels are chosen such that the excitation spectrum one of the labels (the acceptor label) overlaps the emission spectrum of the excited fluorescent label (the donor label). Upon excitation by light within the donor's excitation spectrum, the donor then emits some of the absorbed energy as fluorescent light and dissipates some of the energy by FRET to the acceptor fluorescent label. The fluorescent energy it produces is quenched by the acceptor fluorescent label. FRET can be manifested as a reduction in the intensity of the fluorescent signal from the donor, reduction in the lifetime of its excited state, and re-emission of fluorescent light at the longer wavelengths (lower energies) characteristic of the acceptor (col. 12, lines 36-49). These manifestations of FRET, i.e., reduction in intensity of fluorescence or reduction in lifetime of its excited state or re-emission at longer wavelengths, thus show that the donor label has a pre-complexing fluorescent signature (i.e., an intensity of fluorescence or lifetime of excited state or emission of a particular wavelength) and a post-complexing fluorescent

signature (i.e., a lesser intensity of fluorescence or a shorter lifetime of excited state or re-emission at a longer wavelength).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the FRET assay as taught by Craig et al. in the invention of Myers, Efimov et al. and Chandler et al., because Craig et al. teach that the FRET assay provides the benefit of detecting a protein including whether the protein is modified or unmodified. It is noted that in utilizing the FRET assay as taught by Craig et al. in the invention of Myers, Efimov et al. and Chandler et al., the first and second labels as mentioned above in claim 54, are considered, for example, the donor labels on the different beads, and two additional labels, for example, the acceptor labels, must be utilized, each binding to the respective probe (e.g., protein) on the different beads. It is noted that Applicants' claims do not preclude use of a peptide partner to bind the fluorescent labels to the molecules on the beads, i.e., Applicants' claims do not preclude indirect binding of the fluorescent labels to the molecules on the beads. It is also noted that Applicants disclosure also disclose a FRET assay.

As to claim 59, the pre-complexing and post-complexing fluorescent signature is a first and second, different, fluorescent emission spectrum (see Craig et al., col. 12, lines 48-49).

As to claim 60, the pre-complexing and post-complexing fluorescent signature is a first and second, lifetime measurement (see Craig et al., col. 12, lines 47).

4. Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Myers, 6,267,884, in view of Efimov et al., 7,115,738, and Chandler et al., 6,268,222, as applied to claim 63 above, and further in view of Yon-Hin et al., 6,440,645.

Myers in view of Efimov et al. and Chandler et al. teach the invention substantially as claimed (see above), except for multiple entry ports for analyte delivery, wherein each entry port correlates to a single microfluidic channel. (Myers only disclose an inlet).

However, Yon-Hin et al. disclose a microstructure device for use in assays wherein the device has multiple inlet ports (6), (col. 4, line 61). The diameter of the channels are in the micrometer range (col. 5, lines 63-66) and the device can include pumps (col. 5, line 42) and stationary phase (10), (col. 5, line 44). Yon-Hin et al. teach that the device can be use for fluorescent assays (col. 3, lines 39-41) and chromatographic techniques (col. 5, line 33). It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide multiple inlet ports as taught by Yon-Hin et al. because Yon-Hin et al. teach that such inlet ports allow for assays including fluorescent assays. One of ordinary skill in the art would recognize the benefit of having multiple inlets, such as the ability to introduce various different reagents, and the convenience of having multiple inlets. One of ordinary skill in the art would have reasonable expectation of success in modifying the Myers invention such that there are multiple inlets because Yon-Hin et al. teach that microchannels for assay purposes, such as the Myers column, can have multiple inlets. It is noted that the

multiple inlets are considered to be entry ports and they each correlate to a single microfluidic channel (i.e., they are each openings to a single microfluidic channel).

Response to Arguments

Applicant's arguments with respect to the above rejected claims have been considered but are moot in view of the new ground(s) of rejection. As described above, Myers teaches two populations of beads adjacent to each other as claimed by Applicants.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ann Y. Lam whose telephone number is 571-272-0822. The examiner can normally be reached on Mon.-Fri. 10-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ANN YEN LAM
PATENT EXAMINER

12/2/06